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Title: **Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: Results from PARADIGM-HF**

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ABSTRACT

Background: Compared to heart failure patients with higher systolic blood pressure (SBP), those with lower SBP have a worse prognosis. To make matters worse, the latter patients often do not receive treatment with life-saving therapies that might lower blood pressure further. We examined the association between SBP and outcomes in the Prospective Comparison of angiotensin-receptor blocker-neprilysin inhibitor (ARNI) with an angiotensin converting enzyme (ACE) inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF), as well as the effect of sacubitril/valsartan, compared with enalapril, according to baseline SBP.

Methods: We analyzed the effect of treatment on SBP and on the primary composite outcome (cardiovascular death or heart failure hospitalization), its components and all-cause mortality. We examined baseline SBP as a categorical (<110, 110-<120, 120-<130, 130-<140 and ≥140 mmHg) and continuous variable, as well as average in-trial SBP and time-updated SBP.

Findings: All-cause and cardiovascular mortality rates were highest in patients with the lowest SBP whereas there was a U-shaped relationship between SBP and the rate of heart failure hospitalization. The benefit of sacubitril/valsartan over enalapril was consistent across all baseline SBP categories for all outcomes. For example, the sacubitril/valsartan versus enalapril hazard ratio for the primary endpoint was 0.88 (95%CI 0.74-1.06) in patients with a baseline SBP <110 mmHg and 0.81 (0.65-1.02) for those with a SBP ≥140 mmHg (P for interaction=0.55). Symptomatic hypotension, study drug dose reduction and discontinuation were more frequent in patients with a lower SBP.

Interpretation: In PARADIGM-HF, patients with lower SBP at randomization, notably after tolerating full doses of both study drugs during a run-in period, were at higher risk but generally tolerated sacubitril/valsartan and had the same relative benefit over enalapril as patients with higher baseline SBP.

Key words: heart failure, neprilysin, AT1-receptor, angiotensin, blood pressure

INTRODUCTION

Patients with heart failure often present with low systolic blood pressure (SBP) and because this is associated with poor outcomes, and because physicians are concerned about hypotension, they are often reluctant to prescribe medications likely to lower arterial pressure further, even if such treatments are known to improve prognosis (1-3). Recently, The Prospective Comparison of angiotensin-receptor blocker neprilysin inhibitor (ARNI) with an angiotensin converting enzyme (ACE) inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF) randomized 8399 patients in 47 countries to treatment with enalapril 10 mg twice daily or with sacubitril/valsartan (formerly known as LCZ696) 200 mg twice daily (4,5). Compared with enalapril, sacubitril/valsartan reduced the primary composite endpoint of cardiovascular death or heart failure hospitalization by 20% (5). However, because sacubitril/valsartan not only blocks the renin angiotensin system, but also enhances the activity of vasoactive substances such as the natriuretic peptides and bradykinin, it reduces blood pressure more than an ACE inhibitor or ARB. Because this may cause concern among physicians treating patients with a low SBP, we analyzed the efficacy and safety of sacubitril/valsartan, compared with enalapril, according to baseline SBP, and SBP after randomization, in PARADIGM-HF.

METHODS

The design (4) and the primary results (5,6) have been published. Patients enrolled were in New York Heart Association (NYHA) class II-IV with an ejection fraction ≤40% (changed to ≤35% after amendment) and a plasma B-type natriuretic peptide (BNP) ≥150 pg/ml or N-terminal proBNP (NT-proBNP) ≥600 pg/ml (or for patients with a heart failure hospitalization within 12 months, BNP ≥100 pg/ml or NT-proBNP ≥400 pg/ml). In a run-in period, patients were pre-exposed to an ACE-inhibitor or an angiotensin receptor blocker (ARB) at a dose equivalent to enalapril 10 mg daily for at least 4 weeks before screening. Furthermore, patients had to be on a stable dose of a beta blocker (if tolerated) and a mineralocorticoid antagonist (if indicated). Patients with intolerance to ACE-inhibitors or ARBs, with symptomatic hypotension or a systolic blood pressure <100 mmHg at screening/<95 mmHg at randomization, an estimated glomerular filtration rate (GFR) <30 ml/min/1.73 m^2 or a decrease in eGFR of more than 25% (amended to 35%) between screening and randomization, a serum potassium >5.2 mmol/l at screening (or >5.4 mmol/l at randomization) and a history of angioedema were excluded.

Study procedures

At entry, treatment with an ACE-inhibitor or ARB was stopped (other treatments were continued). Patients first received enalapril 10 mg twice daily for 2 weeks (single-blind) and then sacubitril/valsartan (single-blind) for an additional 3-6 weeks, initially at 100 mg twice daily and then 200 mg twice daily. Patients completing both phases of the active run-in period were assigned in a 1:1 ratio to double-blind treatment with either enalapril 10 mg twice daily or sacubitril/valsartan 200 mg twice daily. If symptomatic hypotension occurred, the protocol recommended reduction in the dose or discontinuation of concomitantly administered blood pressure lowering drugs (e.g.

nitrates and diuretics), except guideline-recommended disease-modifying drugs for heart failure (e.g. beta-blockers and mineralocorticoid receptor antagonists). However, the study drug could also be reduced in dose, or temporarily discontinued, if hypotension (or other adverse effects) occurred. BP was recorded at every visit using a standard sphygmomanometer with an appropriately sized cuff at the non-dominant arm in the sitting position after 5 minutes of rest. During the trial, the occurrence of hypotension was enquired about at each study visit by means of a question on the case report form.

Study outcomes

The main outcomes of interest were the primary endpoint (composite of cardiovascular death and heart failure hospitalization) of the trial and its components, as well as two of the secondary outcomes, all-cause death and the clinical summary score of the Kansas City Cardiomyopathy Questionnaire (KCCQ).

SBP analyses

We analyzed change in SBP from baseline according to treatment assignment, relationship between SBP and clinical outcomes, and effect of study drug on outcomes according to SBP. Specifically, we analyzed change in SBP from baseline to 4 months, and over the whole duration of follow-up, as well as time-updated SBP during follow-up. We analyzed SBP at baseline by category (<110 mmHg, 110-<120 mmHg, 120-<130 mmHg, 130-<140 mmHg and ≥140 mmHg) and as a continuous measure. We examined the association between baseline SBP, change in SBP and time-updated SBP and the primary endpoint and secondary endpoints described above. Finally, we explored the effect of sacubitril/valsartan, compared with enalapril, on these endpoints according to baseline SBP category and SBP analyzed as a

continuous measure. Adverse events according to baseline SBP category are also reported.

Statistical analysis

The effect of sacubitril/valsartan, compared with that of enalapril, on each outcome of interest, according to SBP category, was examined using Cox proportional hazards regression models. Restricted cubic spline analysis was used to examine the effect of treatment according to SBP modeled as a continuous variable. The interaction between continuous SBP and treatment group on the occurrence of the pre-specified safety outcomes was tested in a logistic regression model with a term for interaction between SBP and treatment. All analyses were conducted using R version 3.1.2 . A p-value of <0.05 was considered statistically significant.

RESULTS

Overall, 8399 patients were included in the analysis. Table 1 shows the baseline characteristics of patients in the different SBP categories. Compared to patients with higher SBP, those with lower SBP were younger, more often male and less likely to have an ischemic etiology or a history of diabetes or hypertension. Patients with a lower SBP also had a lower ejection fraction and slightly lower heart rate and body mass index. Notably, NTproBNP and eGFR did not differ substantially across SBP category. Patients with a lower SBP were more often treated with digoxin (not accounted for by differences in prevalence of atrial fibrillation), a MRA and devices.

Effects of enalapril and sacubitril/valsartan on blood pressure

Figure 1 summarizes the change in SBP at 4 months in each treatment group. In both groups, SBP increased in patients with the lowest baseline SBP and decreased in those starting with a higher SBP (Figure 1), a finding that was similar over the whole follow-up period (Supplement Figure 1). However, the increase in SBP with sacubitril/valsartan was less than in the enalapril group and the decrease in SBP with sacubitril/valsartan greater than with enalapril (Supplement Figure 2A), meaning that post-randomization SBP was lower in the sacubitril/valsartan than in the enalapril group across the SBP range (Supplement Figure 2B). At 4 months SBP was approximately 4-6 mmHg lower in the sacubitril/valsartan group across the SBP categories (Supplement Figure 2B).

Relationship between baseline SBP and cardiovascular outcomes

Figure 2 summarizes the relationship between baseline SBP category and clinical outcome (SBP <110 mmHg used as the reference group, hazard ratio=1). Risk was lower for all outcomes in the higher SBP categories although less clearly in patients

with a baseline SBP ≥140 mmHg. In order to investigate this potentially non-linear relationship further, we carried out restricted cubic spline analyses of the association between SBP and the outcomes of interest. Examination of these confirmed that the risk of death (all-cause and cardiovascular) and the risk of heart failure hospitalization was higher in patients with a lower SBP (Figure 3). However, above a SBP of approximately 120mmHg the relationship between SBP and both types of death was flat, whereas the risk of heart failure hospitalization was greater in patients with a higher SBP (>140 mmHg approximately) i.e. there was a U-shaped relationship between SBP and heart failure hospitalization. The *shape* of the relationship between SBP and outcomes was similar in the time-updated covariate analyses (using the last SBP measurement at the time point closest to an event or at the end of the study) (Supplement Figure 3).

Beneficial effects of sacubitril/valsartan compared with enalapril according to baseline SBP

Figure 4 shows the primary endpoint rates by baseline SBP category, according to treatment assignment. Compared with enalapril, sacubitril/valsartan reduced the risk of the primary endpoint across all SBP categories (p-value for SBP-treatment interaction=0.55). Similar findings were observed for cardiovascular death, heart failure hospitalization and all-cause death (Table 2 and Supplement Figures 4-6).

The effects of sacubitril/valsartan, compared with enalapril, on the primary and other outcomes, adjusting for SBP, are summarized in Supplement Figure 7. The effect of treatment was adjusted in a variety of models all of which included age and sex. The models took account of baseline SBP (as a continuous measure), baseline SBP category, average SBP including baseline and all follow-up visits, baseline and post-randomization SBP updated to the time of an event and time-updated SBP group.

These adjustments did not change the benefit of sacubitril/valsartan over enalapril. Furthermore, we analyzed patients with low blood pressure at baseline (<= 100 mm Hg vs. >100 mmHg), who further dropped or increased with SBP on treatment. Supplement Figure 8 shows all cause death (A, sacubitril/valsartan; B, enalapril) and the primary endpoint (C, sacubitril/valsartan; D, enalapril) for low (<= 100 mmHg) or high (> 100 mmHg) SBP at baseline or penultimate. Low SBP at penultimate was clearly associated with high total death on enalapril with lower rates on sacubitril/valsartan. Similar results were obtained with the primary end point (Supplement Figure 8 C,D). Furthermore, we pooled patients and explored high or less (> or ≤ 100 mmHg) at 4 months after randomization to enalapril or sacubitril/valsartan (Supplement Figure 9). The event rates were higher on sacubitril/valsartan and on enalapril when SBP was low. There were less event rates on sacubitril/valsartan than on enalapril in either SBP group.

Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score

At each visit in each SBP group, the portion of patients having a fall of five or more units in the KCCQ clinical summary score was smaller in the sacubitril/valsartan group than in the enalapril group (Table 3). The benefit of sacubitril/valsartan over enalapril in preventing worsening of KCCQ was consistent across SBP groups when adjusted for baseline variables (p for interaction 0.47).

Pre-specified safety assessments according to baseline SBP and treatment assignment

Table 4 summarizes the occurrence of the pre-specified safety outcomes according to SBP at baseline. Symptomatic hypotension and hypotensive symptoms with a SBP <90mmHg were more frequent in the group starting with a SBP <110 mmHg,

irrespective of treatment allocation, although these adverse effects occurred more often in the sacubitril/valsartan group than in the enalapril group. The other adverse effects of interest, including elevation in serum creatinine concentration, did not have an obvious relationship with baseline SBP. Study-drug dose reduction and discontinuation for hypotension was more frequent in patients with a low SBP at baseline (Figure 5). These rates were also nominally higher for sacubitril/valsartan than for enalapril. However, only 1.3% (n=13) of patients discontinued sacubitril/valsartan compared to 9 (1.0%) on enalapril in those with SBP <110 mmHg. The number was $\leq$ 1% in all other baseline SBP groups for both drugs.

DISCUSSION

In this study, we have confirmed and extended prior findings about the relationship between blood pressure and outcomes in patients with heart failure and reduced ejection fraction (HF-REF), albeit in a selected group which had tolerated full-dose enalapril and sacubitril/valsartan during an active run-in period before randomization. We have also described the safety and efficacy of sacubitril/valsartan, compared with enalapril, across the range of blood pressure in PARADIGM-HF. Several studies have shown that patients with low SBP have a worse prognosis than those with higher SBP (1-3).

Because patients with low SBP were often undertreated with disease-modifying therapy, previous studies left open the possibility that sub-optimal treatment, rather than SBP *per se*, accounted for, or at least contributed to, the poor outcomes in these patients. By design, all patients randomized in PARADIGM-HF (5-6) were treated with an evidence-based dose of renin-angiotensin system blocker and more than 90% also received a beta-blocker. Despite this, and greater use of mineralocorticoid receptor antagonists and digoxin, patients with a low BP still had worse outcomes than those with a higher SBP. It is not clear why this was, as patients with low baseline SBP in PARADIGM-HF did not have evidence suggesting more advanced disease. Specifically, patients with lower SBP at baseline were younger and did not have worse NYHA class and KCCQ scores or notably higher natriuretic peptide or lower eGFR levels. LVEF was only slightly lower in patients with lower SBP. Therefore, low SBP is a marker of poor outcome. Whether low SBP identifies patients with more advanced disease and comorbidities and is not necessarily harmful in itself, at least above a certain threshold, could be speculated but cannot be proven.

Interpretation of the relationship between SBP and outcomes in previous studies has also been hampered by the statistical phenomenon of “regression to the mean” whereby SBP was consistently noted to decrease after randomization in patients with a higher starting SBP and to increase in those with a lower baseline SBP *(CHARM (7), Val-HeFT (8), A-HeFT (9) and COPERNICUS(10))*. Potentially, this may have diluted the relationship between baseline SBP and outcomes. For this reason, we also conducted a time-updated covariate analyses, using the last SBP measurement at the time point closest to an event or at the end of the study. Finally, patients with a low SBP on treatment (≤ 100mmHg) had worse outcomes compared to those at higher SBP (>100 mmHg), but the event rate was lower on sacubitril/valsartan compared to enalapril. Whether or to what extend low SBP at baseline, spontaneous decline or drug-induced effects are associated if not involved with poor outcome cannot be clarified. These findings strengthened the relationship between SBP and outcome, reinforcing the importance of SBP as a predictor of outcome.

The third extension of prior findings is our demonstration of a U-shaped relationship between SBP and heart failure hospitalization (and therefore the composite of cardiovascular death or heart failure hospitalization) whereby higher hospitalization rates were observed at both ends of the SBP range included in PARADIGM-HF (5). This was quite different than for mortality (cardiovascular or all-cause) where the relationship between SBP and the risk of death was flat above a SBP of approximately 120mmHg. Indeed, it was notable that 14% of patients in PARADIGM-HF had a SBP above the threshold for treatment of hypertension (i.e. those in the ≥140 mmHg category, with a mean SBP of 148 mmHg), despite their treatment with

multiple hypotensive medications. Why the rate of hospitalization of heart failure was higher in patients with a SBP ≥140 mmHg, but mortality was not, is unclear.

Sacubitril/valsartan improved clinical outcomes, compared with enalapril, across the range of SBP studied. This treatment benefit was robust, persisting after adjustment for SBP at baseline, average SBP during follow-up and time-updated SBP, the latter, as explained above, strengthening the relationship between low SBP and poor outcomes. Consequently, even in patients with a persistently low SBP after treatment, sacubitril/valsartan was superior to enalapril in reducing mortality and morbidity.

In these analyses, patients with a low baseline SBP are those of most interest given their greater risk of death and hospitalization and the concern physicians often have about using blood pressure lowering drugs in them. Indeed, because of this concern, patients with a low SBP have even been excluded from many key trials in heart failure (*CIBIS-2, MERIT-HF*). PARADIGM-HF enrolled a large number (n=1747) of patients with a low SBP (1747 <110, 1173 <105 and 309 <100mmHg), comparing favorably with other major trials that have examined the safety and tolerability of blood pressure reducing drugs in heart failure, including Val-HeFT (1156 patients ≤110 mmHg), COPERNICUS (396 <105 mmHg), and CHARM (385 ≤100 mmHg).[7,8,10] Patients in the lowest SBP category in PARADIGM-HF attained the same *relative* magnitude of benefit from sacubitril/valsartan as patients in the trial overall. Consequently, because such patients are at higher risk of adverse clinical outcomes, the same *relative* risk reduction with sacubitril/valsartan is expected to give a greater *absolute* risk reduction – of the order of a 3-4 fewer fatal and non-fatal events per 1000 patient years of treatment. This principle is true for all disease

modifying neurohumoral and vasodilating drugs studied to date yet, paradoxically, as mentioned earlier, these sicker patients with potentially more to gain are the least likely to be treated. Inevitably, however, this additional benefit comes at a cost. As in prior studies, patients with a low baseline SBP have more hypotension-related adverse effects reported, irrespective of treatment allocation (even if assigned to placebo). This was also observed in PARADIGM-HF, although the proportion of patients assigned to sacubitril/valsartan and experiencing symptoms of hypotension and a SBP <90 mmHg or discontinuing study drug for hypotension was not large. However, this finding must be interpreted in light of the study design (with sequential active run-in periods – enalapril followed by sacubitril/valsartan). Specifically, of 10513 patients treated with enalapril over a median duration of 15 [IQR 14-21] days run-in 1102 (10.5%) discontinued the study for any reason (including administrative reasons and withdrawal of consent). For sacubitril/valsartan, of 9419 patients treated over a median duration of 29 [IQR 26-35] days run-in 977 (10.4%) discontinued the study. In the two periods, 146 and 164 patients respectively, discontinued for an adverse effect related to hypotension. A recent analysis, using inverse probability weighting to adjust for variables associated with discontinuation during the run-in, showed no significant diminution of the benefit of sacubitril/valsartan over enalapril with respect to the key outcomes cardiovascular death, heart failure hospitalization and all-cause death was shown (11). Furthermore, in another study without an active run-in period (TITRATION), up to 84% of patients tolerated the introduction of sacubitril/valsartan without interruption or down-titration (12).

Some limitations of our study need to be acknowledged. This was a *post-hoc* exploratory analysis and patients were not randomized according to SBP. All randomized patients had demonstrated toleration of both enalapril 10mg twice daily

followed by sacubitril/valsartan 200 mg twice daily. Patients could not be randomized if their SBP was <95 mmHg or they had symptoms of hypotension.

In conclusion, we have confirmed that low SBP is associated with worse outcomes in HF-REF and have shown that, if an individual could tolerate sacubitril/valsartan, (notably after pre-exposure to the maximal dose in a run-in phase) it was beneficial across the range of SBP included in PARADIGM-HF in patients taking other guideline recommended therapies (11). Compared to patients with a higher SBP, those with lower SBP may obtain greater absolute benefits from sacubitril/valsartan but at the expense of more hypotension-related adverse effects.

REFERENCES

1. Ambrosy AP, Vaduganathan M, Mentz RJ, Greene SJ, Subačius H, Konstam MA, Maggioni AP, Swedberg K, Gheorghiade M. Clinical profile and prognostic value of low systolic blood pressure in patients hospitalized for heart failure with reduced ejection fraction: insights from the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial. Am Heart J 2013;165:216-25.

2. Gheorghiade M, Vaduganathan M, Ambrosy A, Böhm M, Campia U, Cleland JG, Fedele F, Fonarow GC, Maggioni AP, Mebazaa A, Mehra M, Metra M, Nodari S, Pang PS, Ponikowski P, Sabbah HN, Komajda M, Butler J. Current management and future directions for the treatment of patients hospitalized for heart failure with low blood pressure. Heart Fail Rev 2013;18:107-22.

3. Komajda M, Böhm M, Borer JS, Ford I, Robertson M, Manolis AJ, Tavazzi L, Swedberg K; SHIFT Investigators. Efficacy and safety of ivabradine in patients with chronic systolic heart failure according to blood pressure level in SHIFT. Eur J Heart Fail 2014;16:810-6.

4. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Eur J Heart Fail 2013;15:1062-73.

5. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.

6. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile M, Andersen K, Arango JL, Arnold JM, Bělohlávek J, Böhm M, Boytsov S, Burgess LJ, Cabrera W, Calvo C, Chen CH, Dukat A, Duarte YC, Erglis A, Fu M, Gomez E, Gonzàlez-Medina A, Hagège AA, Huang J, Katova T, Kiatchoosakun S, Kim KS, Kozan Ö, Llamas EB, Martinez F, Merkely B, Mendoza I, Mosterd A, Negrusz-Kawecka M, Peuhkurinen K, Ramires FJ, Refsgaard J, Rosenthal A, Senni M,

Sibulo AS Jr, Silva-Cardoso J, Squire IB, Starling RC, Teerlink JR, Vanhaecke J, Vinereanu D, Wong RC; PARADIGM-HF Investigators and Coordinators. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation 2015;131:54-61.

7. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767-71.

8. Reed SD, Friedman JY, Velazquez EJ, Gnanasakthy A, Califf RM, Schulman KA. Multinational economic evaluation of valsartan in patients with chronic heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 2004;148:122-8.

9. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN; African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049-57.

10. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe

chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002;106:2194-9.

11. Desai AS, Solomon S, Claggett B, McMurray JJ, Rouleau J, Swedberg K, Zile M, Lefkowitz M, Shi V, Packer M. Factors associated with noncompletion during the run-in period before randomization and influence on the estimated benefit of LCZ696 in the PARADIGM-HF trial. Circ Heart Fail 2016;9:e002735.

12. Senni M, McMurray JJ, Wachter R, McIntyre HF, Reyes A, Majercak I, Andreka P, Shehova-Yankova N, Anand I, Yilmaz MB, Gogia H, Martinez-Selles M, Fischer S, Zilahi Z, Cosmi F, Gelev V, Galve E, Gómez-Doblas JJ, Nociar J, Radomska M, Sokolova B, Volterrani M, Sarkar A, Reimund B, Chen F, Charney A. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. Eur J Heart Fail 2016;doi: 10.1002/ejhf.548.

13. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides

P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Jung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803-69.

LEGENDS TO FIGURES

Figure 1

Change in systolic blood pressure at 4 months according to systolic blood pressure categories at baseline enalapril (left) and LCZ696 (right) treated patients. Patients with extreme increases or decreases in these groups are depicted separately.

Figure 2

Adjusted hazard ratios for the primary endpoint (A), cardiovascular death (B), heart failure hospitalization (C) and total death (D) according to systolic blood pressure at baseline in all patients. The group with systolic blood pressure <110 mmHg is given as a reference (=1).

Figure 3

Hazard ratio for the primary outcome (A), cardiovascular death (B), heart failure hospitalization (C) and all-cause death (D) in all patients (left), on enalapril (middle) and on LCZ696 (right) according to systolic blood pressure at baseline.

Figure 4

Kaplan Meier event curves for the primary endpoint <110 mmHg (A), 110-<120 mmHg (B), 120-<130 mmHg (C), 130-<140mmHg (D) and ≥140 mmHg (E) on enalapril and LCZ696. Cox regression p-values and the interaction p-value are given.

Figure 5

Hypotension (A), rate of dose adjustments (B) and rate of dose adjustments + discontinuation of study drugs (C) on enalapril (left) or LCZ696.

Supplement Figure 1

Systolic blood pressure change from baseline over time in all patients (A), on enalapril (B) and on LCZ696 (C) according to baseline blood pressure.

Supplement Figure 2

Systolic blood pressure after 4 months according to baseline systolic blood pressure (A) and change in systolic blood pressure at 4 months according to baseline systolic blood pressure (B). Lines of identity (A) and neutrality (B) are depicted by the dotted lines.

Supplement Figure 3

Adjusted hazard ratios for the primary endpoint (A), cardiovascular death (B), heart failure hospitalization (C) and total death (D) according to time-updated systolic blood pressure in all patients. The group with systolic blood pressure <110 mmHg is given as reference (=1).

Supplement Figure 4

Kaplan Meier event curves for cardiovascular death by baseline SBP groups <110 mmHg (A), 110-<120 mmHg (B), 120-<130 mmHg (C), 130-<140mmHg (D) and >140 mmHg (E) on enalapril and LCZ696. Cox regression p-values and the interaction p-value are given.

Supplement Figure 5

Kaplan Meier event curves for heart failure hospitalization by baseline SBP groups <110 mmHg (A), 110-<120 mmHg (B), 120-<130 mmHg (C), 130-<140mmHg (D) and >140 mmHg (E) on enalapril and LCZ696. Cox regression p-values and the interaction p-value are given.

Supplement Figure 6

Kaplan Meier event curves for total death by baseline SBP groups <110 mmHg (A), 110-<120 mmHg (B), 120-<130 mmHg (C), 130-<140mmHg (D) and >140 mmHg (E) on enalapril and LCZ696. Cox regression p-values and the interaction p-value are given.

Supplement Figure 7

Hazard ratios showing the treatment effect of LCZ696 on the primary endpoint (A), cardiovascular death (B), heart failure hospitalization (C) and total death (D) adjusted for systolic blood pressure at baseline (all individual patients) (LCZ base_num) by different baseline blood pressure groups (LCZ base_grp) by the average of systolic blood pressure at all visits (LCZ Avg_num) and time-updated blood pressure by all individuals (LCZ update_num) and updated systolic blood pressure by groups (LCZ update_grp). The risk on enalapril is given as reference.

Supplement Figure 8

Kaplan Meier event curves for all cause death (A,B) and the primary endpoint (C,D) on sacubitril/valsartan (A,C) or enalapril (B,D) by low systolic blood pressure (SBP) at baseline (<=100 mmHg (low) versus >100 mmHg, high) and low or high on treatment.

Supplement Figure 9

Kaplan Meier event curves for the primary endpoint (A,B), cardiovascular death (C,D) and heart failure hospitalization (E,F) on sacubitril/valsartan (left, A,C,E) or enalapril (right, B,D,F) with a blood pressure performance above (blue, high) or below (red, low) 100 mmHg at 4 months.

Table 1 Baseline characteristics according to systolic blood pressure

Variable	Statistic	<110 (N = 1747)	110-<120 (N = 1931)	120-<130 (N = 2059)	130-<140 (N = 1477)	≥140 (N = 1185)	P value
Sacubitril/valsartan	N (%)	834 (47.7%)	990 (51.3%)	1041 (50.6%)	731 (49.5%)	591 (49.9%)	0.2714
Age	Mean (SD)	61.30 (12.01)	62.81 (11.58)	64.34 (11.17)	65.65 (10.36)	65.83 (10.89)	<0.0001
Sex Female	N (%)	335 (19%)	389 (20%)	441 (21%)	359 (24%)	308 (26%)	<0.0001
Race White	N (%)	941 (53.9%)	1218 (63.1%)	1441 (70.0%)	1070 (72.4%)	874 (73.8%)	<0.0001
Black	N (%)	111 (6.4%)	101 (5.2%)	92 (4.5%)	54 (3.7%)	70 (5.9%)	0.0039
Asian	N (%)	453 (25.9%)	392 (20.3%)	320 (15.5%)	205 (13.9%)	139 (11.7%)	<0.0001
Other	N (%)	242 (13.9%)	220 (11.4%)	206 (10.0%)	148 (10.0%)	102 (8.6%)	<0.0001
Region North American	N (%)	181 (10.4%)	165 (8.5%)	137 (6.7%)	67 (4.5%)	52 (4.4%)	<0.0001
Latin America	N (%)	357 (20.4%)	381 (19.7%)	331 (16.1%)	212 (14.4%)	152 (12.8%)	<0.0001
Western Europe	N (%)	510 (29.2%)	467 (24.2%)	442 (21.5%)	321 (21.7%)	311 (26.2%)	<0.0001
Central Europe	N (%)	258 (14.8%)	526 (27.2%)	832 (40.4%)	672 (45.5%)	538 (45.4%)	<0.0001
Asia-Pacific	N (%)	441 (25.2%)	392 (20.3%)	317 (15.4%)	205 (13.9%)	132 (11.1%)	<0.0001
SBP	Mean (SD)	102.18 (3.77)	112.66 (3.02)	122.76 (3.01)	132.45 (2.90)	147.73 (9.16)	<0.0001
DBP	Mean (SD)	64.86 (7.31)	70.31 (7.63)	75.21 (7.93)	78.48 (8.33)	82.88 (10.00)	<0.0001
eGFR	Mean (SD)	67.09 (20.86)	67.96 (20.80)	67.71 (20.28)	67.95 (18.74)	67.87 (19.21)	0.6947
BNP	Median (IQR)	263.9 [157.7, 520.8]	251.0 [158.5, 482.9]	243.3 [145.6, 455.2]	243.9 [148.6, 442.2]	262.6 [161.4, 447.4]	0.0103
NTproBNP	Median (IQR)	1765.0 [939.0, 3520.0]	1606.0 [893.0, 3322.0]	1597.5 [867.0, 3140.0]	1578.5 [836.0, 3000.0]	1600.0 [900.0, 3120.0]	0.3009
HR	Mean (SD)	71.26 (12.21)	72.09 (11.69)	72.70 (11.99)	73.33 (12.07)	72.57 (12.06)	<0.0001
BMI	Mean (SD)	27.24 (5.41)	27.74 (5.46)	28.28 (5.41)	28.75 (5.52)	29.28 (5.66)	<0.0001
Creatinine (mg/dl)	Mean (SD)	1.15 (0.30)	1.13 (0.29)	1.12 (0.30)	1.10 (0.30)	1.10 (0.30)	<0.0001

Variable	Statistic	<110 (N = 1747)	110-<120 (N = 1931)	120-<130 (N = 2059)	130-<140 (N = 1477)	≥140 (N = 1185)	P value
Ischaemic etiology	N (%)	949 (54.3%)	1194 (61.8%)	1231 (59.8%)	923 (62.5%)	739 (62.4%)	<0.0001
HF duration 0-1 yrs	N (%)	514 (29.4%)	562 (29.1%)	636 (30.9%)	468 (31.7%)	343 (28.9%)	0.3536
>1-5 yrs	N (%)	627 (35.9%)	752 (38.9%)	768 (37.3%)	580 (39.3%)	505 (42.6%)	0.0041
>5 yrs	N (%)	606 (34.7%)	617 (32.0%)	655 (31.8%)	429 (29.0%)	337 (28.4%)	0.0014
Ejection fraction (%)	Mean (SD)	27.58 (6.49)	28.84 (6.27)	30.01 (6.01)	30.62 (5.89)	31.03 (5.65)	<0.0001
NYHA I	N (%)	111 (6.4%)	96 (5.0%)	80 (3.9%)	43 (2.9%)	59 (5.0%)	<0.0001
II	N (%)	1315 (75.4%)	1396 (72.4%)	1402 (68.2%)	992 (67.2%)	814 (68.8%)	<0.0001
III	N (%)	310 (17.8%)	431 (22.4%)	556 (27.1%)	428 (29.0%)	293 (24.8%)	<0.0001
IV	N (%)	7 (0.4%)	5 (0.3%)	17 (0.8%)	14 (0.9%)	17 (1.4%)	0.0011
KCCQ-Clinical	Median (IQR)	82.3 [66.7, 93.8]	82.3 [65.6, 92.7]	79.2 [62.5, 91.7]	77.9 [60.4, 90.6]	78.1 [60.4, 91.1]	<0.0001
Hypertension	N (%)	892 (51.1%)	1219 (63.1%)	1526 (74.1%)	1244 (84.2%)	1059 (89.4%)	<0.0001
Diabetes	N (%)	503 (28.8%)	671 (34.7%)	709 (34.4%)	546 (37.0%)	478 (40.3%)	<0.0001
Atrial Fibrillation	N (%)	605 (34.6%)	672 (34.8%)	795 (38.6%)	589 (39.9%)	430 (36.3%)	0.0031
Prior HF Hospitalization	N (%)	1081 (61.9%)	1223 (63.3%)	1333 (64.7%)	921 (62.4%)	716 (60.4%)	0.1265
MI	N (%)	725 (41.5%)	915 (47.4%)	877 (42.6%)	632 (42.8%)	485 (40.9%)	9e-04
Stroke	N (%)	151 (8.6%)	143 (7.4%)	194 (9.4%)	132 (8.9%)	105 (8.9%)	0.2340
CABG	N (%)	263 (15.1%)	343 (17.8%)	304 (14.8%)	217 (14.7%)	176 (14.9%)	0.0444
PCI	N (%)	385 (22.0%)	490 (25.4%)	430 (20.9%)	272 (18.4%)	224 (18.9%)	<0.0001
ACE inhibitor	N (%)	1356 (77.6%)	1531 (79.3%)	1641 (79.7%)	1140 (77.2%)	864 (72.9%)	1e-04
ARB	N (%)	395 (22.6%)	408 (21.1%)	425 (20.6%)	334 (22.6%)	330 (27.8%)	<0.0001

Variable	Statistic	<110 (N = 1747)	110-<120 (N = 1931)	120-<130 (N = 2059)	130-<140 (N = 1477)	≥140 (N = 1185)	P Value
Diuretic	N (%)	1403 (80.3%)	1538 (79.6%)	1656 (80.4%)	1202 (81.4%)	939 (79.2%)	0.6564
Digoxin	N (%)	601 (34.4%)	596 (30.9%)	640 (31.1%)	403 (27.3%)	299 (25.2%)	<0.0001
Beta-Blocker	N (%)	1609 (92.1%)	1805 (93.5%)	1918 (93.2%)	1373 (93.0%)	1106 (93.3%)	0.5383
Mineralocortoid	N (%)	1082 (61.9%)	1140 (59.0%)	1154 (56.0%)	745 (50.4%)	550 (46.4%)	<0.0001
Anticoagulant	N (%)	545 (31.2%)	603 (31.2%)	723 (35.1%)	471 (31.9%)	343 (28.9%)	0.0041
Antiplatelet	N (%)	999 (57.2%)	1122 (58.1%)	1116 (54.2%)	828 (56.1%)	671 (56.6%)	0.1435
Lipid Lowering	N (%)	988 (56.6%)	1117 (57.8%)	1134 (55.1%)	840 (56.9%)	650 (54.9%)	0.3568
ICD	N (%)	349 (20.0%)	343 (17.8%)	279 (13.6%)	160 (10.8%)	112 (9.5%)	<0.0001
CRT	N (%)	181 (10.4%)	151 (7.8%)	134 (6.5%)	58 (3.9%)	50 (4.2%)	<0.0001

SBP – systolic blood pressure (mmHg)
DBP – diastolic blood pressure (mmHg)
eGFR - Estimated GFR (ml/min/1.73m2)
HR- heart rate (bpm)
BMI – body mass index (kg/m^2)
MI – myocardial infarction
CABG – coronary artery bypass grafting
PCI – percutaneous coronary intervention
ACE – angiotensin converting enzyme
ARB – angiotensin receptor blocker
ICD- implantable cardioverter defibrillator
CRT – cardiac resynchronization therapy

Table 2

		Primary Endpoint					CV Death				
SBP-Group	Treat	Events	Rate/100yrs (CI)	HR (CI)	P-value	P for interaction	Events	Rate/100yrs (CI)	HR (CI)	P-value	P for interaction
All	Enalapril	1117	13.2 (12.4, 13.9)	0.80 (0.73-0.87)			693	7.5 (7.0, 8.1)	0.80 (0.71-0.89)	0.0001	
	Sac/val	914	10.5 (9.8, 11.2)				558	6.0 (5.5, 6.5)			
<110	Enalapril	249	14.0 (12.3, 15.8)	0.88 (0.74-1.06)	0.1918		164	8.6 (7.3, 10.0)	0.84 (0.66-1.05)	0.1289	
	Sac/val	208	12.3 (10.7, 14.1)				130	7.1 (6.0, 8.5)			
110-<120	Enalapril	249	13.3 (11.7, 15.1)	0.84 (0.70-1.01)	0.0579		148	7.2 (6.1, 8.5)	0.88 (0.70-1.11)	0.2741	
	Sac/val	223	11.2 (9.7, 12.7)				136	6.3 (5.3, 7.5)			
120-<130	Enalapril	264	12.6 (11.1, 14.2)	0.73 (0.61-0.87)	0.0006		173	7.7 (6.6, 8.9)	0.65 (0.52-0.82)	0.0003	
	Sac/val	202	9.2 (8.0, 10.5)				118	5.0 (4.2, 6.0)			
130-<140	Enalapril	190	12.3 (10.7, 14.2)	0.74 (0.59-0.92)	0.0058		116	6.9 (5.7, 8.3)	0.79 (0.60-1.04)	0.0967	
	Sac/val	141	9.1 (7.6, 10.7)				90	5.5 (4.4, 6.7)			
>=140	Enalapril	165	13.6 (11.6, 15.9)	0.81 (0.65-1.02)	0.0674	0.5542	92	6.8 (5.5, 8.4)	0.91 (0.68-1.22)	0.5368	0.3580
	Sac/val	140	11.0 (9.2, 13.0)				84	6.2 (4.9, 7.7)			

		HF-Hospitalization					Total Death				
SBP-Group	Treat	Events	Rate/100yrs (CI)	HR (CI)	P-value	P for interaction	Events	Rate/100yrs (CI)	HR (CI)	P-value	P for interaction
All	Enalapril	658	7.7 (7.2, 8.4)	0.80 (0.71-0.89)	0.0001		835	9.0 (8.4, 9.7)	0.84 (0.76-0.93)	0.0009	
	Sac/val	537	6.2 (5.6, 6.7)				11	7.6 (7.1, 8.2)			
<110	Enalapril	152	8.5 (7.2, 10.0)	0.91 (0.71-1.15)	0.4455		195	10.2 (8.8, 11.7)	0.85 (0.69-1.05)	0.1348	
	Sac/val	131	7.7 (6.5, 9.2)				158	8.7 (7.4, 10.2)			
110-<120	Enalapril	147	7.9 (6.7, 9.3)	0.85 (0.67-1.07)	0.1666		186	9.1 (7.8, 10.5)	0.84 (0.68-1.04)	0.1107	
	Sac/val	133	6.7 (5.6, 7.9)				164	7.6 (6.5, 8.9)			
120-<130	Enalapril	153	7.3 (6.2, 8.6)	0.75 (0.59-0.95)	0.0192		203	9.0 (7.8, 10.4)	0.75 (0.61-0.92)	0.0062	
	Sac/val	121	5.5 (4.6, 6.6)				159	6.8 (5.8, 7.9)			
130-<140	Enalapril	108	7.0 (5.8, 8.5)	0.69 (0.51-0.93)	0.0138		142	8.4 (7.1, 9.9)	0.83 (0.65-1.06)	0.1306	
	Sac/val	75	4.8 (3.8, 6.0)				115	7.0 (5.8, 8.4)			
>=140	Enalapril	98	8.1 (6.6, 9.9)	0.75 (0.56-1.01)	0.0611	0.5753	109	8.1 (6.6, 9.7)	1.05 (0.81-1.37)	0.704	0.4092
	Sac/val	77	6.0 (4.8, 7.6)				115	8.5 (7.0, 10.2)			

Table 3 Five unit fall from baseline in KCCQ clinical summary score at each in trial visit

Variable	Statistic	<110 E* (N = 913)	<110 S/V** (N = 834)	110-<120 E* (N = 941)	110-<120 S/V** (N = 990)	120-<130 E* (N = 1018)	120-<130 S/V** (N = 1041)	130-<140 E* (N = 746)	130-<140 S/V** (N = 731)	≥140 E* (N = 594)	≥140 S/V** (N = 591)
Month 4	N_{obs} (N_{miss})	743 (170)	692 (142)	793 (148)	836 (154)	880 (138)	912 (129)	648 (98)	633 (98)	507 (87)	510 (81)
Yes	N (%)	210 (28.3%)	176 (25.4%)	212 (26.7%)	241 (28.8%)	233 (26.5%)	214 (23.5%)	172 (26.5%)	154 (24.3%)	138 (27.2%)	124 (24.3%)
No	N (%)	533 (71.7%)	516 (74.6%)	581 (73.3%)	595 (71.2%)	647 (73.5%)	698 (76.5%)	476 (73.5%)	479 (75.7%)	369 (72.8%)	386 (75.7%)
Month 8	N_{obs} (N_{miss})	717 (196)	678 (156)	761 (180)	811 (179)	838 (180)	868 (173)	618 (128)	614 (117)	488 (106)	489 (102)
Yes	N (%)	229 (31.9%)	183 (27.0%)	246 (32.3%)	226 (27.9%)	262 (31.3%)	231 (26.6%)	181 (29.3%)	157 (25.6%)	149 (30.5%)	144 (29.4%)
No	N (%)	488 (68.1%)	495 (73.0%)	515 (67.7%)	585 (72.1%)	576 (68.7%)	637 (73.4%)	437 (70.7%)	457 (74.4%)	339 (69.5%)	345 (70.6%)
Month 12	N_{obs} (N_{miss})	668 (245)	647 (187)	731 (210)	774 (216)	804 (214)	848 (193)	599 (147)	591 (140)	463 (131)	469 (122)
Yes	N (%)	220 (32.9%)	170 (26.3%)	227 (31.1%)	234 (30.2%)	248 (30.8%)	243 (28.7%)	181 (30.2%)	179 (30.3%)	139 (30.0%)	147 (31.3%)
No	N (%)	448 (67.1%)	477 (73.7%)	504 (68.9%)	540 (69.8%)	556 (69.2%)	605 (71.3%)	418 (69.8%)	412 (69.7%)	324 (70.0%)	322 (68.7%)
Month 24	N_{obs} (N_{miss})	359 (554)	377 (457)	401 (540)	440 (550)	502 (516)	494 (547)	365 (381)	366 (365)	287 (307)	300 (291)
Yes	N (%)	123 (34.3%)	119 (31.6%)	154 (38.4%)	133 (30.2%)	152 (30.3%)	152 (30.8%)	137 (37.5%)	108 (29.5%)	104 (36.2%)	90 (30.0%)
No	N (%)	236 (65.7%)	258 (68.4%)	247 (61.6%)	307 (69.8%)	350 (69.7%)	342 (69.2%)	228 (62.5%)	258 (70.5%)	183 (63.8%)	210 (70.0%)
Month 36	N_{obs} (N_{miss})	114 (799)	125 (709)	152 (789)	158 (832)	210 (808)	188 (853)	138 (608)	138 (593)	126 (468)	114 (477)
Yes	N (%)	46 (40.4%)	42 (33.6%)	71 (46.7%)	47 (29.7%)	71 (33.8%)	60 (31.9%)	55 (39.9%)	60 (43.5%)	46 (36.5%)	45 (39.5%)
No	N (%)	68 (59.6%)	83 (66.4%)	81 (53.3%)	111 (70.3%)	139 (66.2%)	128 (68.1%)	83 (60.1%)	78 (56.5%)	80 (63.5%)	69 (60.5%)
End of study	N_{obs} (N_{miss})	680 (233)	637 (197)	715 (226)	752 (238)	809 (209)	834 (207)	574 (172)	579 (152)	451 (143)	450 (141)
Yes	N (%)	319 (46.9%)	251 (39.4%)	315 (44.1%)	282 (37.5%)	357 (44.1%)	317 (38.0%)	253 (44.1%)	229 (39.6%)	198 (43.9%)	211 (46.9%)
No	N (%)	361 (53.1%)	386 (60.6%)	400 (55.9%)	470 (62.5%)	452 (55.9%)	517 (62.0%)	321 (55.9%)	350 (60.4%)	253 (56.1%)	239 (53.1%)

*E=enalapril **S/V=sacubitril/valsartan

Table 4 Adverse Events during Randomized Treatment

Variable		<110 E* (N = 913)	<110 S/V** (N = 834)	110-<120 E* (N = 941)	110-<120 S/V** (N = 990)	120-<130 E* (N = 1018)	120-<130 S/V** (N = 1041)	130-<140 E* (N = 746)	130-<140 S/V** (N = 731)	≥140 E* (N = 594)	≥140 S/V** (N = 591)	P value
Symptomatic Hypotension	N (%)	125 (13.7%)	213 (25.5%)	101 (10.7%)	143 (14.4%)	87 (8.5%)	119 (11.4%)	50 (6.7%)	66 (9.0%)	25 (4.2%)	47 (8.0%)	<0.0001
Symptomatic Hypotension SBP <90mmHg	N (%)	26 (2.8%)	59 (7.1%)	18 (1.9%)	25 (2.5%)	10 (1.0%)	15 (1.4%)	5 (0.7%)	9 (1.2%)	0 (0.0%)	4 (0.7%)	<0.0001
Creatinine >= 2.5 mg/dL	N (%)	42 (4.6%)	32 (3.8%)	47 (5.0%)	25 (2.5%)	46 (4.5%)	42 (4.0%)	26 (3.5%)	17 (2.3%)	27 (4.5%)	23 (3.9%)	0.0637
Creatinine > 3.0 mg/dL	N (%)	15 (1.6%)	13 (1.6%)	22 (2.3%)	11 (1.1%)	17 (1.7%)	18 (1.7%)	15 (2.0%)	10 (1.4%)	14 (2.4%)	11 (1.9%)	0.6590
Potassium > 5.5 mmol/L	N (%)	149 (16.3%)	114 (13.7%)	146 (15.5%)	152 (15.4%)	201 (19.7%)	203 (19.5%)	136 (18.2%)	118 (16.1%)	102 (17.2%)	94 (15.9%)	0.0089
Potassium > 6.0 mmol/L	N (%)	39 (4.3%)	28 (3.4%)	53 (5.6%)	40 (4.0%)	64 (6.3%)	51 (4.9%)	51 (6.8%)	31 (4.2%)	29 (4.9%)	31 (5.2%)	0.0306
Cough	N (%)	164 (18.0%)	133 (15.9%)	145 (15.4%)	118 (11.9%)	127 (12.5%)	100 (9.6%)	99 (13.3%)	69 (9.4%)	66 (11.1%)	54 (9.1%)	<0.0001
Angioedema												
No treatment/antihistamines only	N (%)	4 (0.4%)	1 (0.1%)	2 (0.2%)	2 (0.2%)	0 (0.0%)	4 (0.4%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	2 (0.3%)	0.3498
Catecholamines/ corticosteroids without hospitalization	N (%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	2 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	3 (0.5%)	0.3010

Hospitalized/no airway compromise	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0.3472
Airway compromise	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-

*E=enalapril **S/V=sacubitril/valsartan

Figure 1

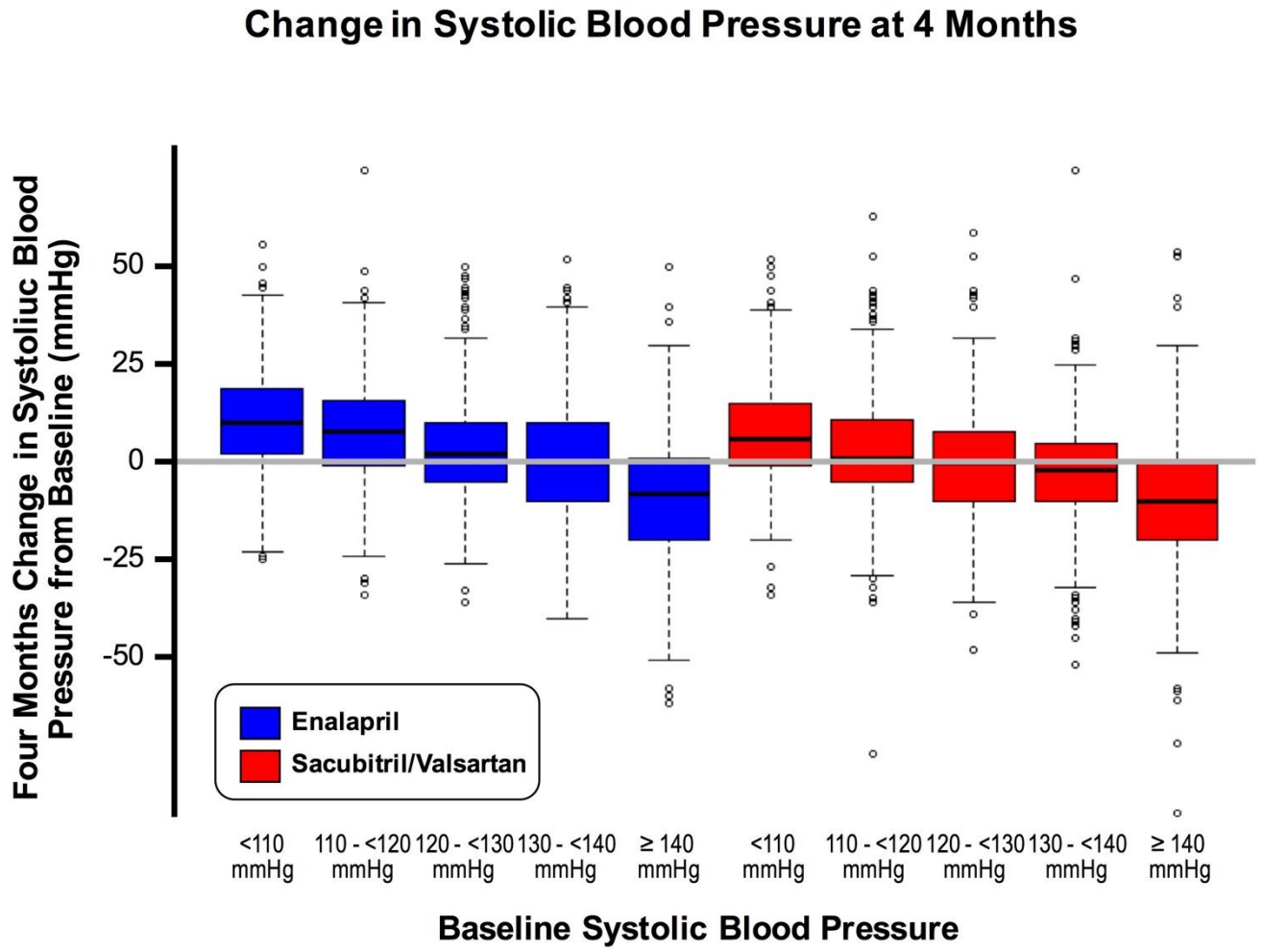

Change in Systolic Blood Pressure at 4 Months
Four Months Change in Systoliuc Blood Pressure from Baseline (mmHg)
50
25
0
-25
-50
Enalapril
Sacubitril/Valsartan
<110 mmHg
110 - <120 mmHg
120 - <130 mmHg
130 - <140 mmHg
≥ 140 mmHg
<110 mmHg
110 - <120 mmHg
120 - <130 mmHg
130 - <140 mmHg
≥ 140 mmHg
Baseline Systolic Blood Pressure

Figure 2 **Hazard Ratios by Systolic Blood Pressure Groups**

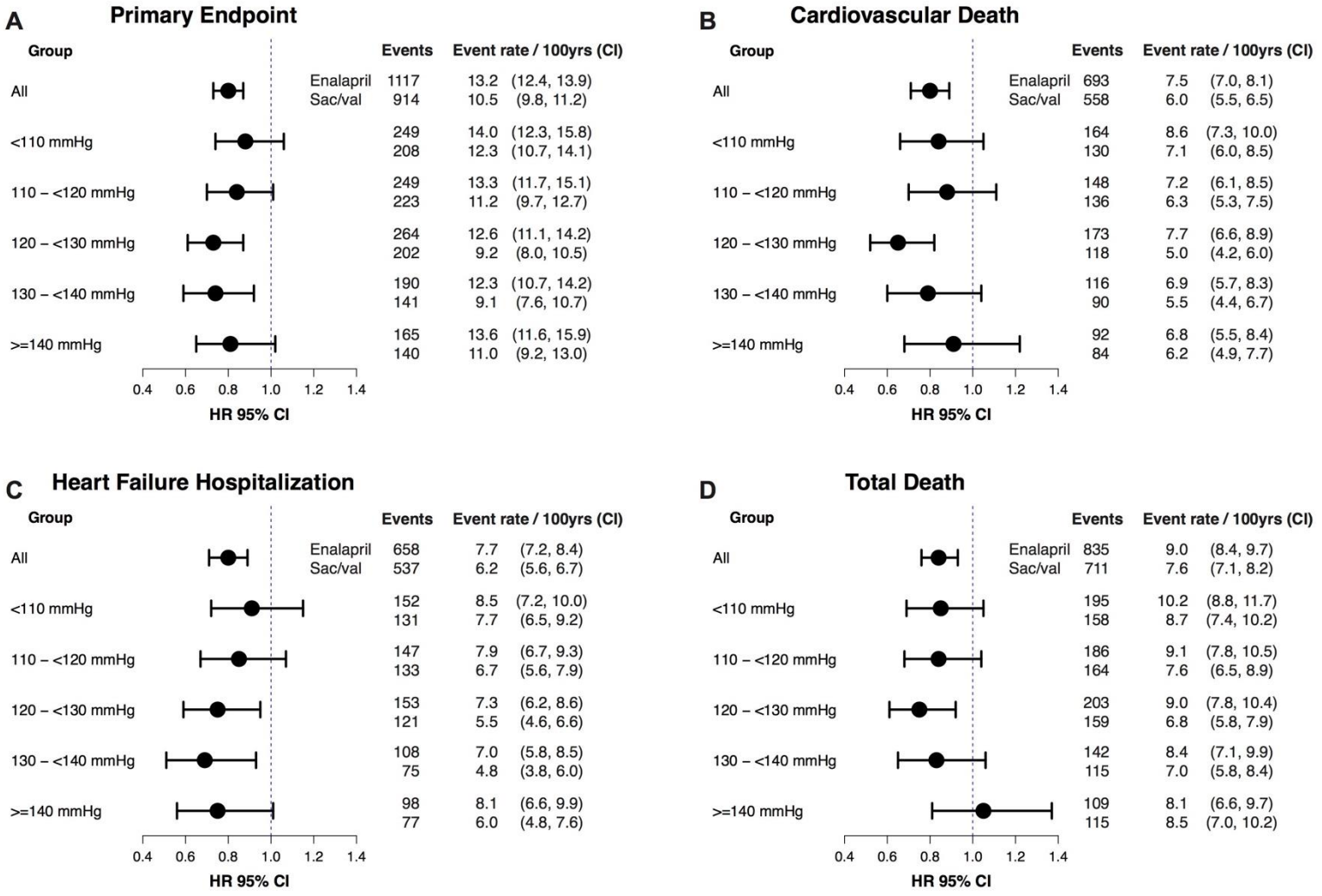


Figure 3

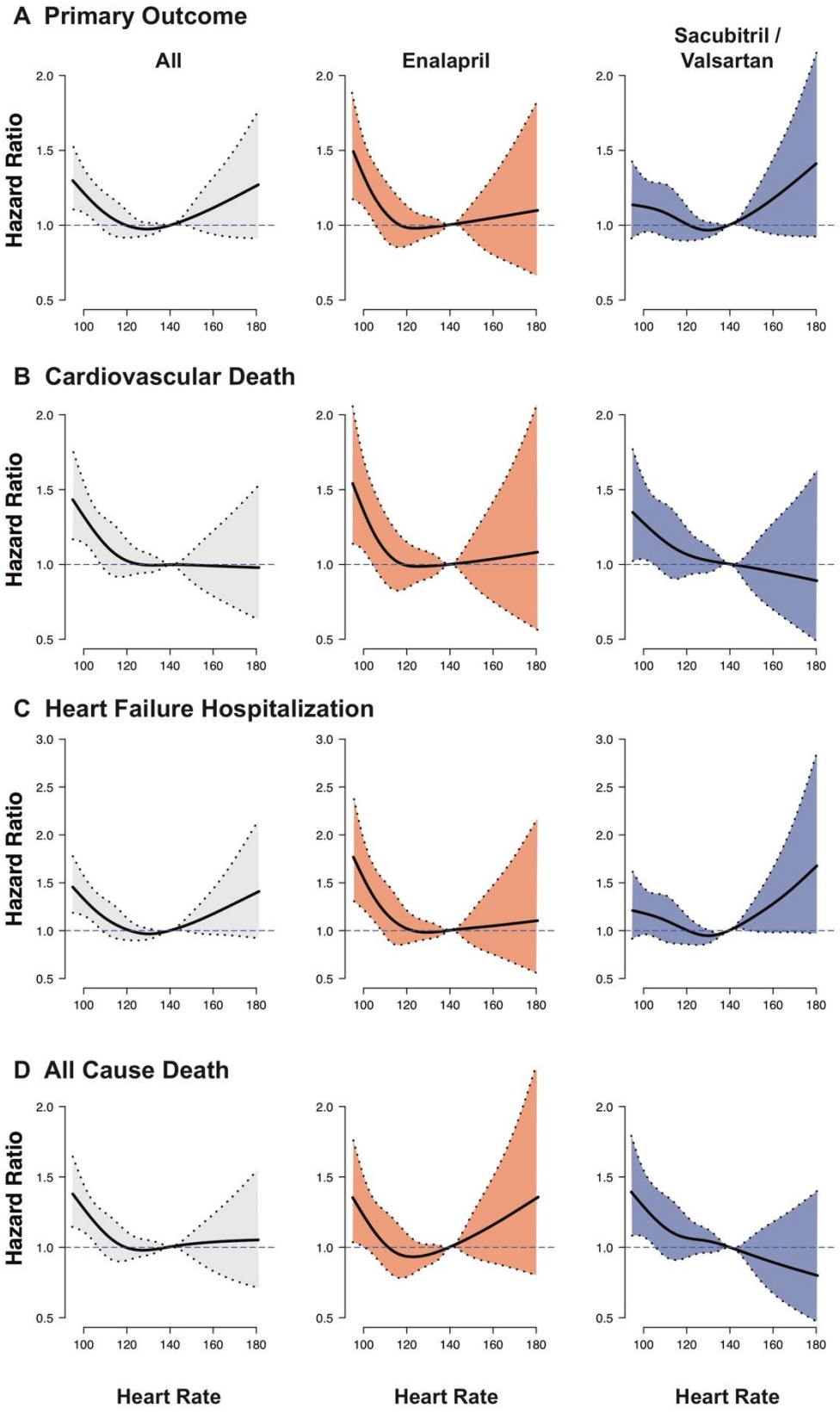
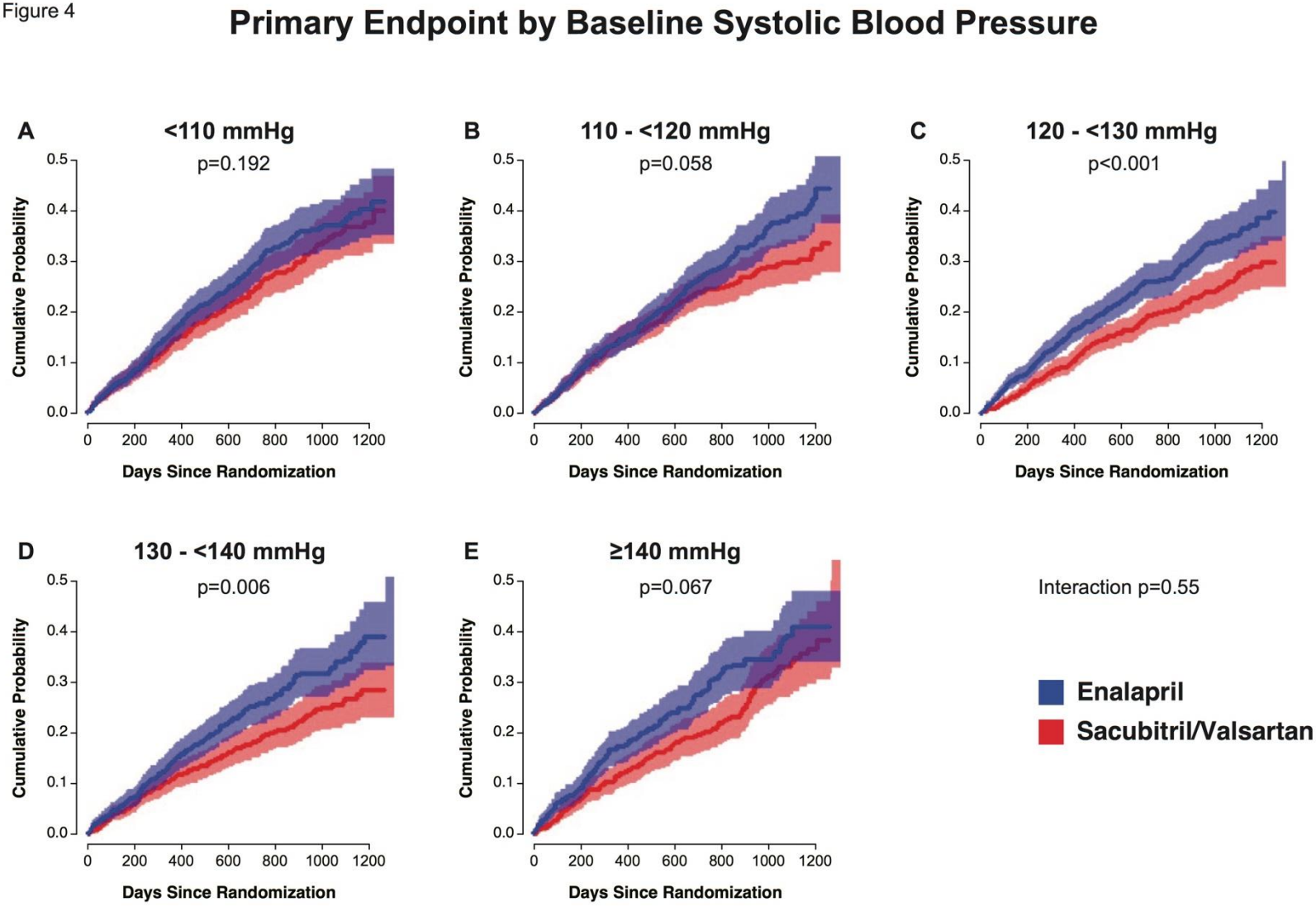

A Primary Outcome
All
Enalapril
Sacubitril / Valsartan
B Cardiovascular Death
C Heart Failure Hospitalization
D All Cause Death
Hazard Ratio
Heart Rate
100
120
140
160
180
0.5
1.0
1.5
2.0
2.5
3.0

Figure 4


Primary Endpoint by Baseline Systolic Blood Pressure
A
<110 mmHg
p=0.192
B
110 - <120 mmHg
p=0.058
C
120 - <130 mmHg
p<0.001
D
130 - <140 mmHg
p=0.006
E
≥140 mmHg
p=0.067
Cumulative Probability
0.0
0.1
0.2
0.3
0.4
0.5
0
200
400
600
800
1000
1200
Days Since Randomization
Interaction p=0.55
Enalapril
Sacubitril/Valsartan

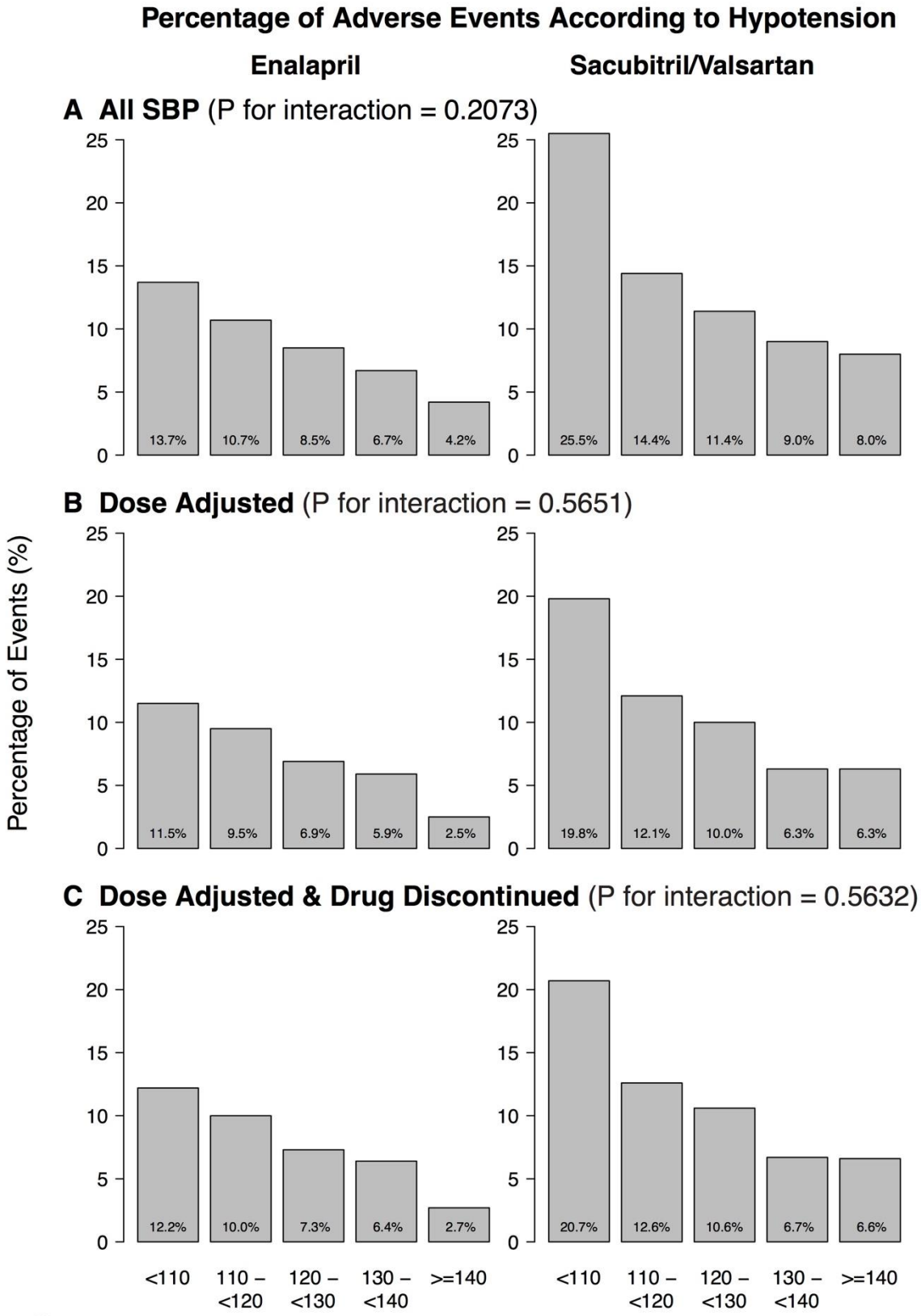
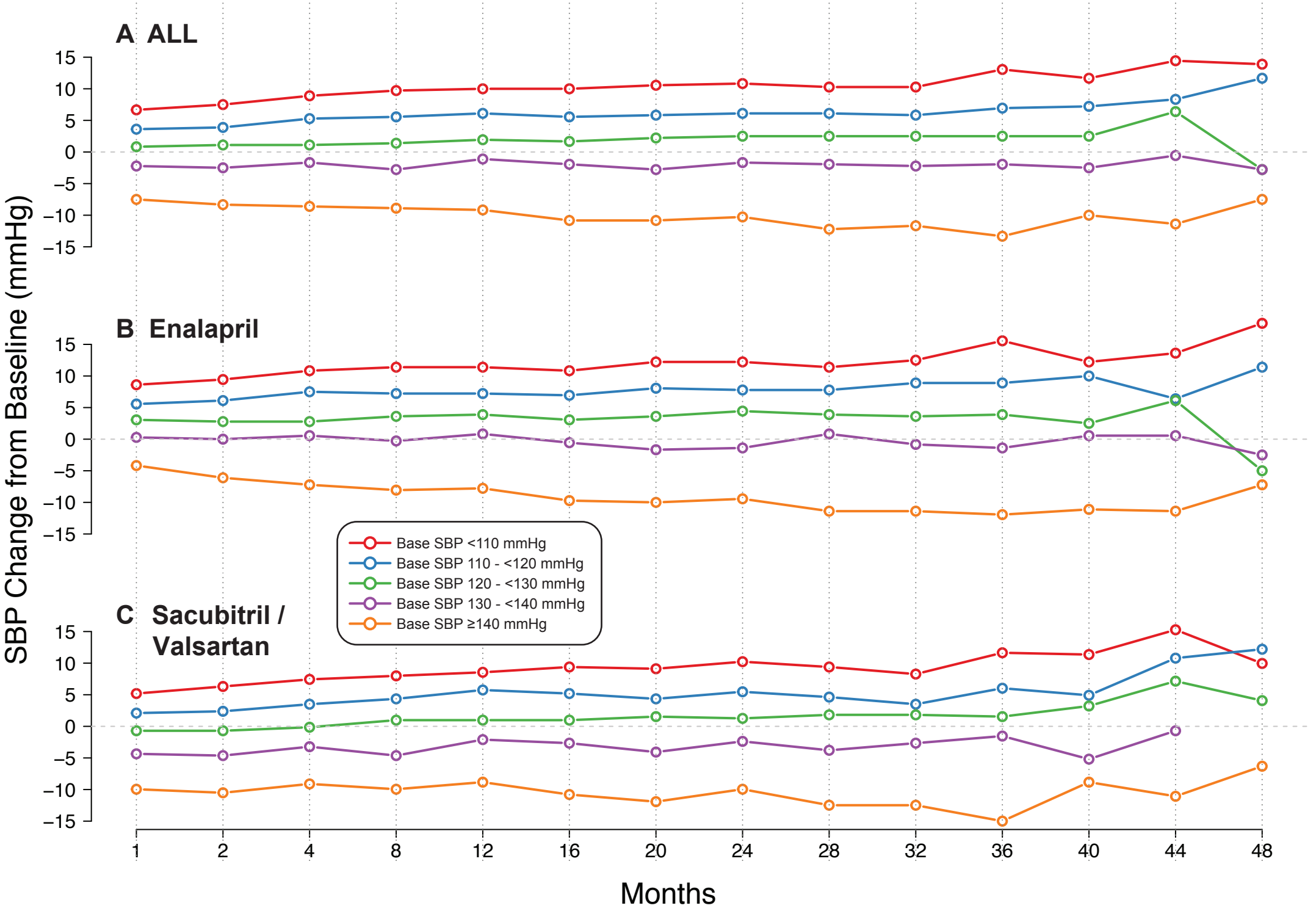

Percentage of Adverse Events According to Hypotension
Enalapril
Sacubitril/Valsartan
A All SBP (P for interaction = 0.2073)
B Dose Adjusted (P for interaction = 0.5651)
C Dose Adjusted & Drug Discontinued (P for interaction = 0.5632)
Percentage of Events (%)
0
5
10
15
20
25
13.7%
10.7%
8.5%
6.7%
4.2%
25.5%
14.4%
11.4%
9.0%
8.0%
11.5%
9.5%
6.9%
5.9%
2.5%
19.8%
12.1%
10.0%
6.3%
6.3%
12.2%
10.0%
7.3%
6.4%
2.7%
20.7%
12.6%
10.6%
6.7%
6.6%
<110
110 – <120
120 – <130
130 – <140
>=140

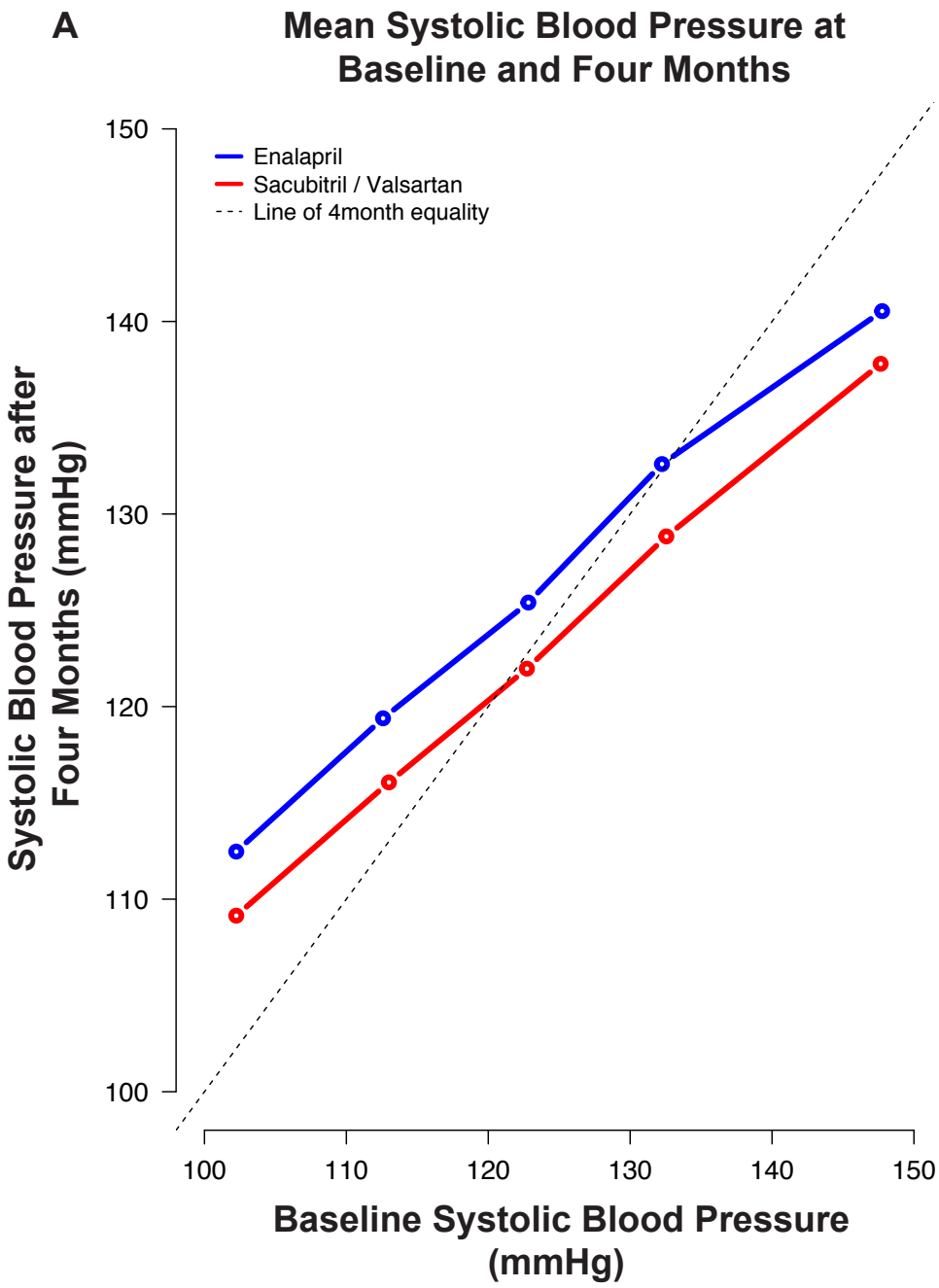
Figure 5

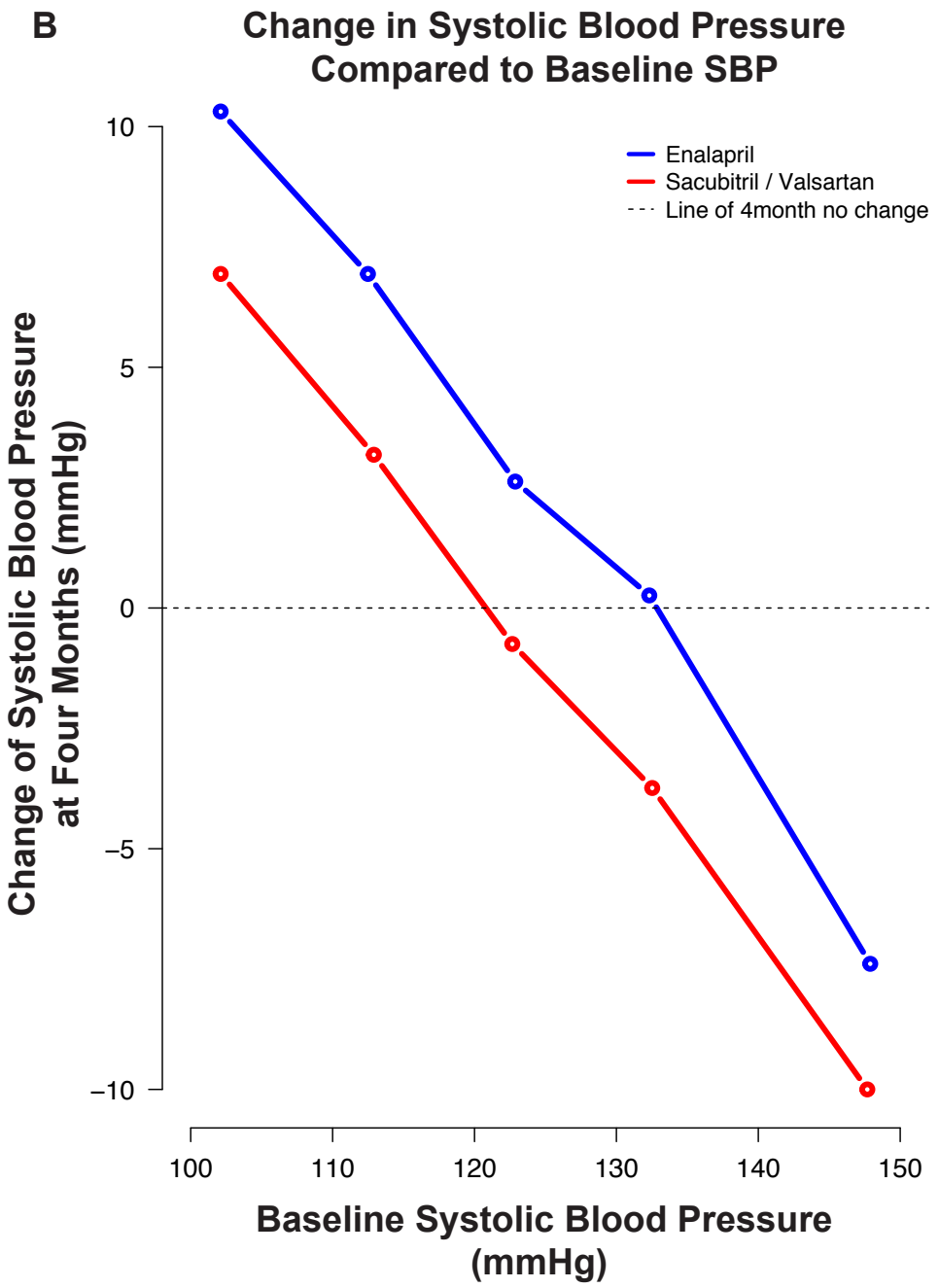
Suppl. Figure 1

Systolic Blood Pressure Drugs According to Baseline SBP

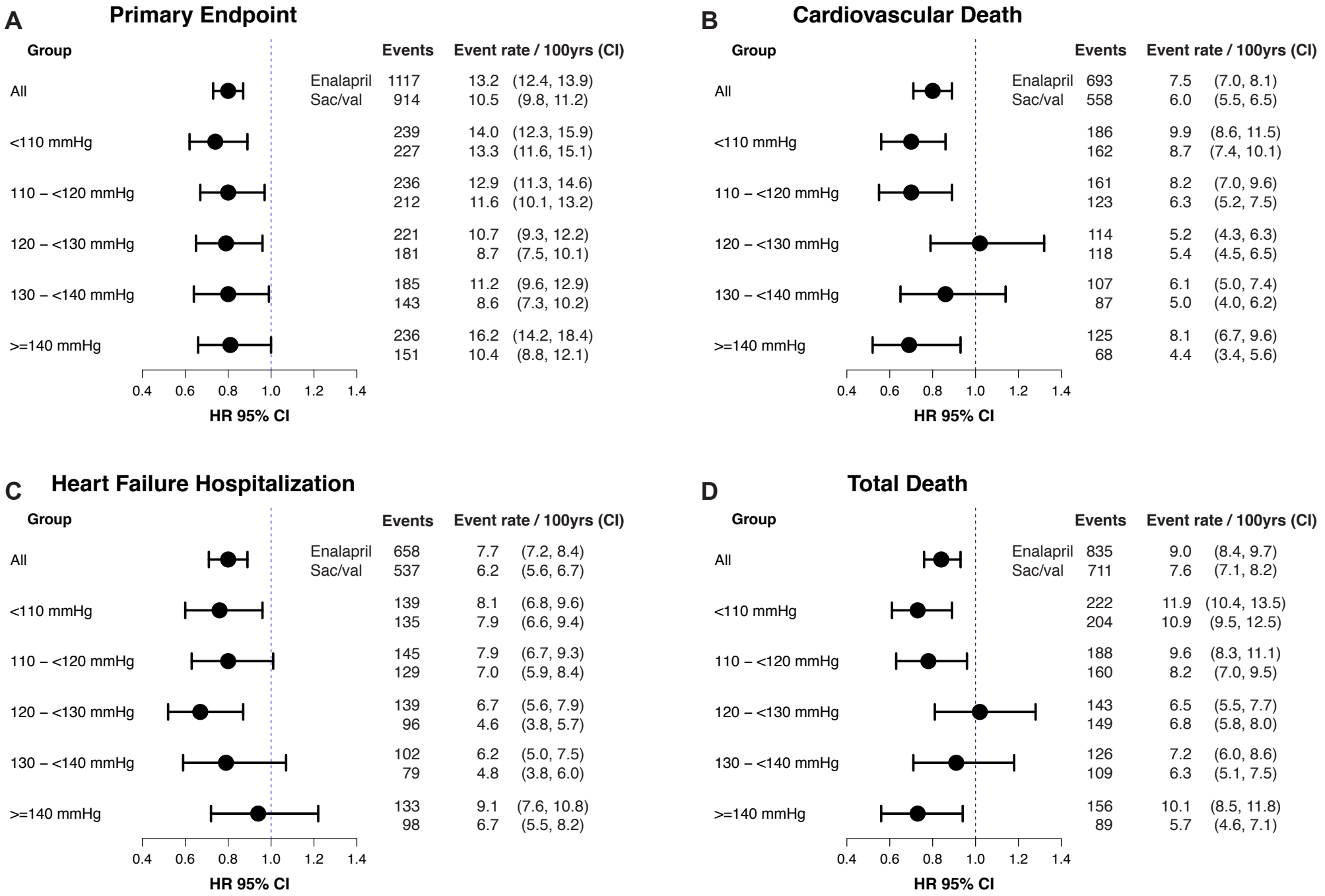


Suppl. Figure 2



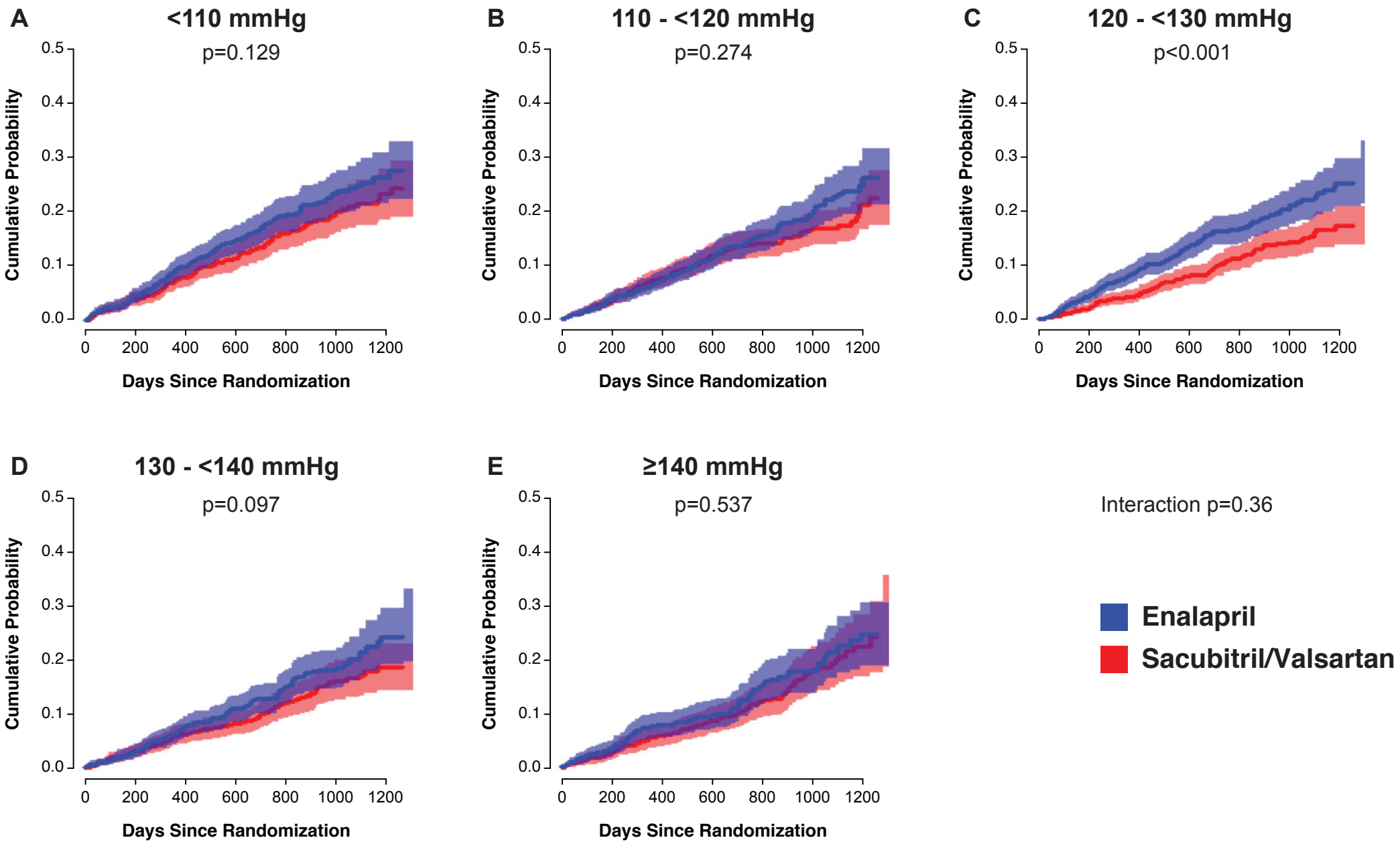


Suppl. Figure 3 **Hazard Ratios by Time Updated Systolic Blood Pressure Groups**



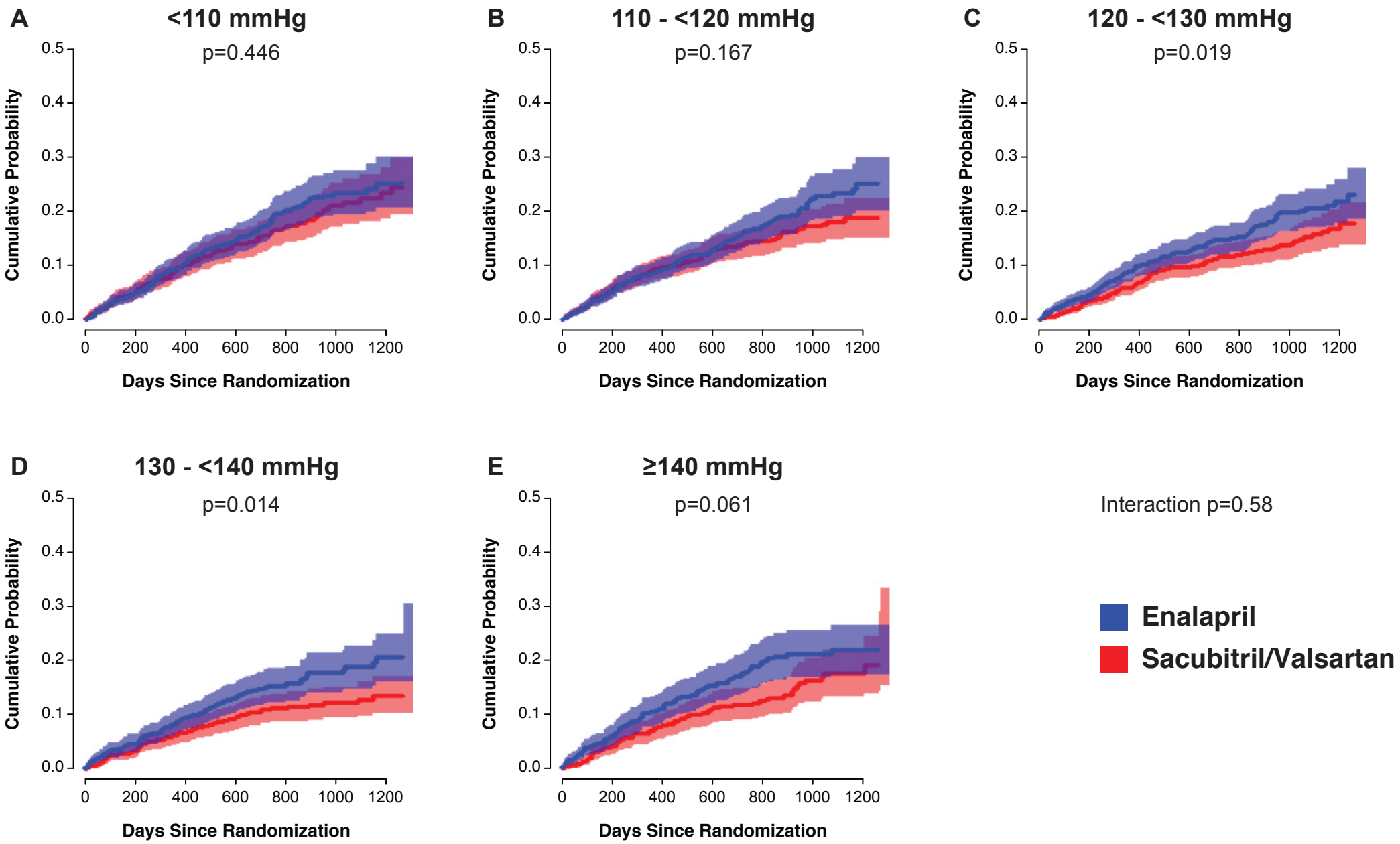
Suppl. Figure 4

Cardiovascular Death by Baseline SBP Group



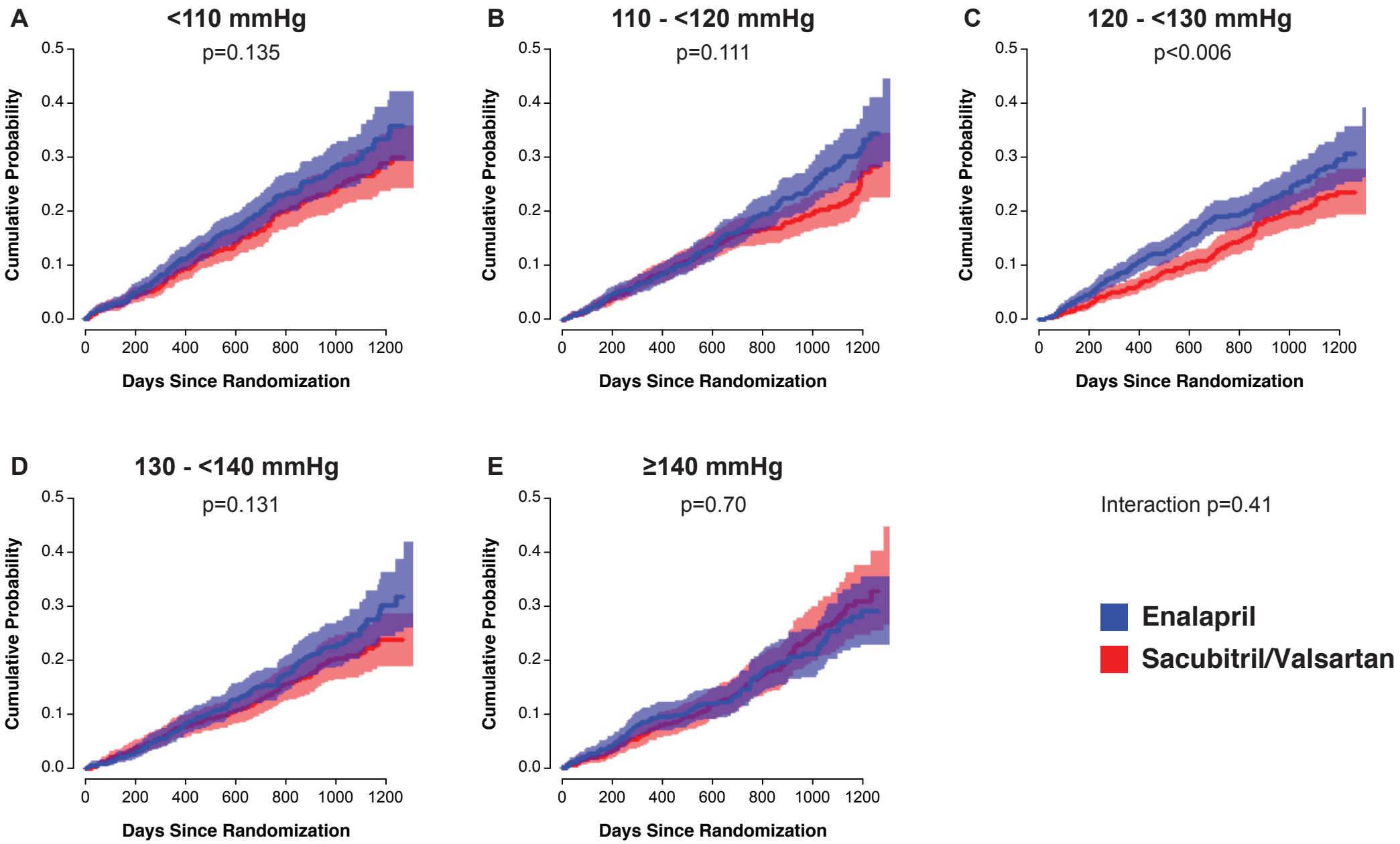
Suppl. Figure 5

Hospitalization for Heart Failure by Baseline SBP Group



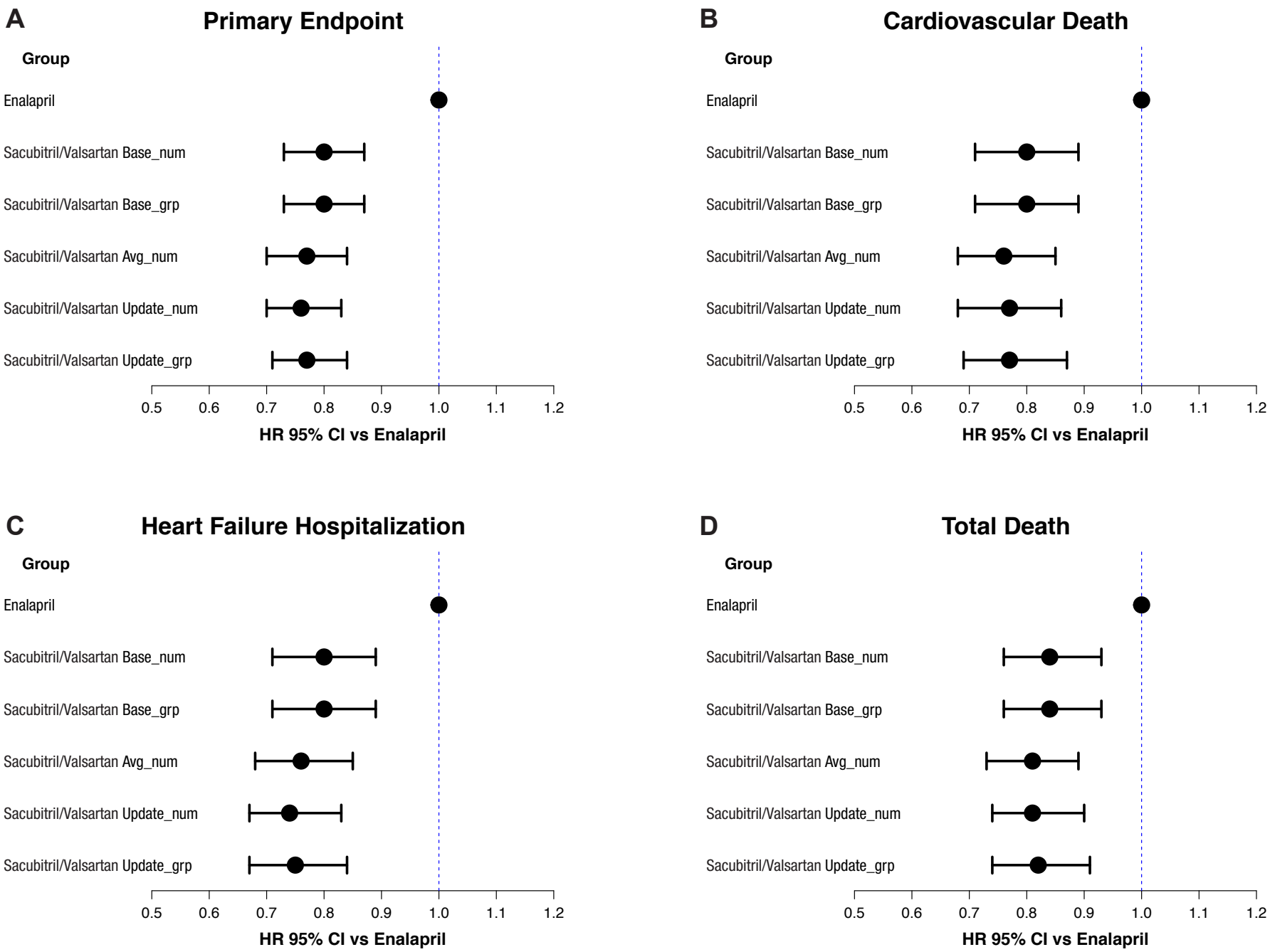
Suppl. Figure 6

Total Death by Baseline SBP Group

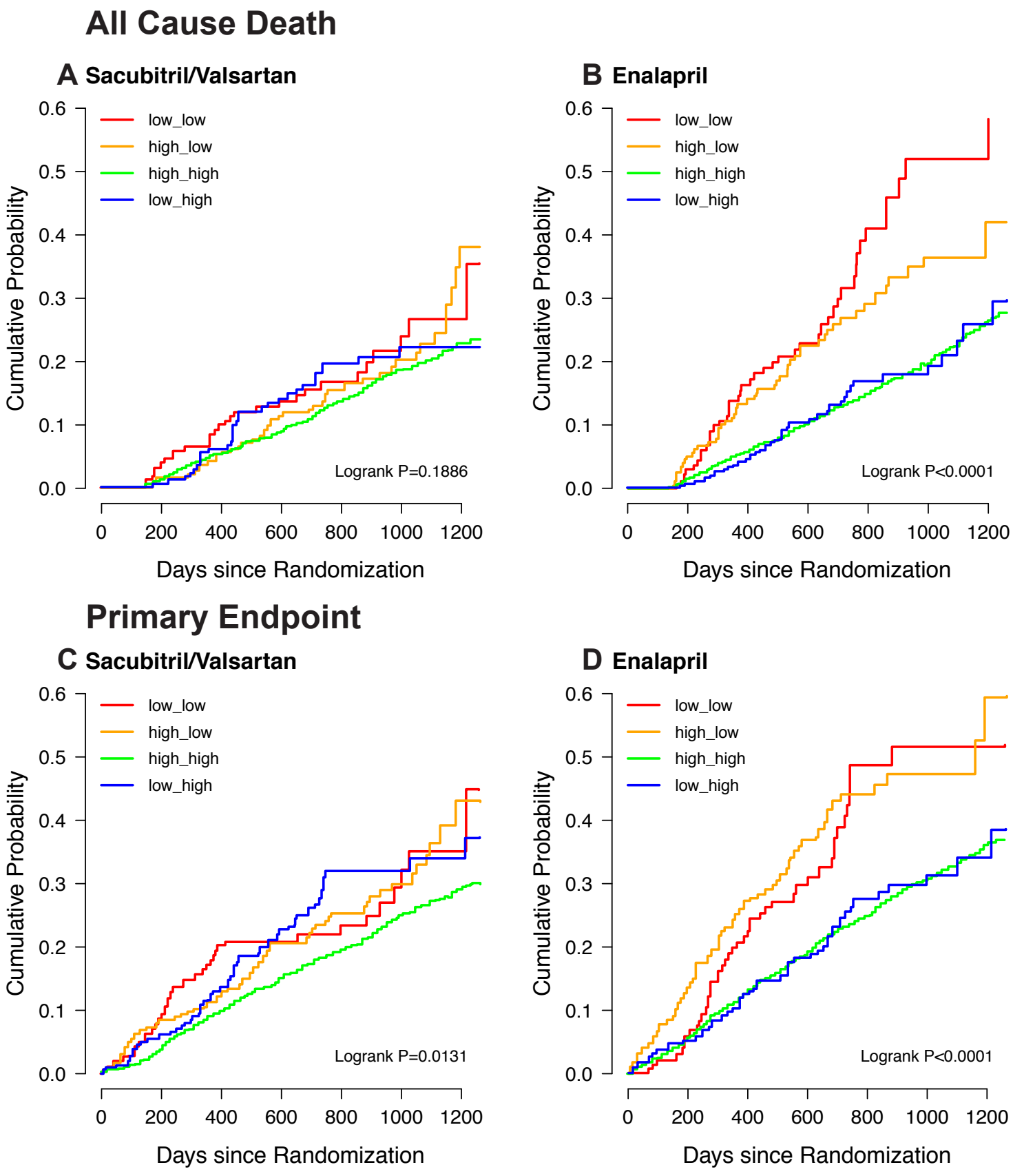


Suppl. Figure 7

Hazard Ratios by Treatment Groups



Supplement Figure 8



Suppl. Figure 9 - Systolic blood pressure 4 months after baseline